Measuring vascular properties using contrast agents

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1. Introduction

The objective of this lecture is to describe how vascular properties and function can be measured by using MR contrast agents. This will include:

- The properties of tumours that lend themselves to assessment using contrast.
- The transport and delivery of contrast agents.
- Contrast agent properties.
- Imaging methods to assess signal change due to contrast agent delivery.
- The trade-offs inherent in measuring contrast agent uptake by MRI.
- What properties of tumours are measured.
- Examples of applications in cancer.

The use of modelling to extract physiological imaging is the subject of the following lecture, and the experimental use of these and similar techniques are also covered in a separate lecture.

2. Vascular properties of tumours

Tumour development is the result of a complex process of mutations, changes in cellular regulation and selection processes. One or more mutations in DNA (either inherited or somatic) can lead to failure of normal growth control mechanisms, and the ability of an aberrant cell to continually grow. Up to a certain point, this can proceed on the basis of oxygen and nutrient diffusion. Folkman(1) proposed that above a size of around 1mm, a vascular supply was required to provide continued nutrient support, and that tumours that grew above this size had evolved the capacity to develop their own blood supply. It is now clear that growth factor support of vascular development is an important characteristic of most larger tumours, and that neo-angiogenesis, the enhancement of local blood supply to feed a tumour, is largely controlled by stress derived processes(2). Tumour cells, driven by local hypoxia as they have outgrown their blood supply, up-regulate proteins such as HIF-1α leading to the production of vascular endothelial growth factor, creating a gradient of concentration in tissues surrounding tumour. This has the effect of causing the vascular endothelium of nearby blood vessels to bud new capillaries that are leaky and which are VEGF dependent, without smooth muscle, which progressively grow towards the tumour. This results in the establishment of a characteristic rich but disorganised vascular network, that can have high blood volume and has large endothelial junctions. Recent work is showing that similar effects occur in the lymphatic system(3). When the stress factors are reduced, due to the additional vasculature, VEGF generation can cease, resulting in apoptosis of this neo-vasculature, a reduction in or trimming of vascular support, with tissue necrosis and a subsequent further cycle of neo-angiogenesis. This continual remodelling increases the chaotic environment of the tumour, as well as maintaining evolutionary pressure on the cancer cells. These processes also favour the breakdown of parts of the matrix supporting tumour cells, the development of increased motility, and the ingress of

tumour cells into the vascular and lymphatic systems. Often the tumour is characterised by high interstitial pressure due to an imbalance between vascular leakiness, and lymphatic drainage, which can also affect vascular delivery. Thus important factors include areas of high perfusion, leaky vasculature, areas of low perfusion, chaotic and disordered vasculature, high blood volume in some areas, high interstitial pressure.

3. Transport and delivery of contrast agents

Currently most low molecular weight contrast agents are administered by intravenous bolus in clinical studies, and animal studies often use tail vein injection. Where high time resolution methods are used (1-10s acquisition periods) a power injector is preferred to ensure a well defined and reproducible bolus, aiding assessment of first pass and initial uptake. Some modelling methods obtain most information from the washout phase and in this case a slower IV infusion may be used. Higher molecular weight agents may also require a slower IV infusion. The use of a primed line, and following the bolus with a saline flush is important with bolus injections, to ensure full delivery of the contrast agent into the vascular system. Following injection, the contrast agent will make a first pass of the heart and lungs, resulting in mixing, dilution and lengthening of the bolus. Subsequently, it will pass through the heart again, and be distributed by the arterial system. The arrival function in a tissue network will depend on the cardiac output and on the flow dynamics *en route*, which may be expected to lengthen the bolus in proportion to distance and gauge of vessels. In a tumour the chaotic nature of the vasculature may be expected to further lengthen this function, which may show a regional variation, and will also be affected by local interstitial pressure. First pass studies provide information on delivery to the tumour. Leakage out of the vessels will dependent on the characteristics of the vascular endothelium (permeability, area), the properties of the contrast agent, and the driving gradient (blood concentration, extracellular space). These properties may change within the 10-100 μm range. These processes will affect the initial portion of the contrast agent uptake curve. Further uptake is then defined by the continuing relative blood to interstitial space concentration gradient. Once this reverses, washout can occur, but this will usually be at a much slower rate, as the concentration gradient will generally be small. Blood concentration is governed by cardiac output, uptake in other tissues and excretion (eg renal). Some of these characteristics can be affected by disease or treatment.

4. Contrast agent properties

Small molecular weight contrast agents, containing chelated gadolinium, have been most widely used. There are small differences between different chelates that may affect uptake in specific tissues, or excretion(4). Gd-DTPA is the best characterised contrast agent, and the agent for which plasma clearance curve data are incorporated in the most widely used Tofts-Kermode model. Modelling using other contrast agents would need to ensure that appropriate data are used. Likewise care should be exercised in combining data from measurements using different agents, although they may have similar characteristics. Small molecular weight compounds leak very quickly in tumours and more slowly in many normal tissues. They do not leak through the blood brain barrier unless it is disrupted.

Higher molecular weight agents may use gadolinium or superparamagnetic particles. Larger compounds may include a large number of gadolinium molecules. Examples include albumin bound gadolinium, USPIOs, contrast agents with multiple

gadolinium binding sites, and higher molecular weight agents with limited binding sites(5). These may act blood pool agents, with reduced leakage even in tumour; or provide agents that leak more slowly. In all cases they have much increased relaxivity, leading to a higher sensitivity of detection. They may be used to improve the accuracy and sensitivity of first pass studies, provided they can be delivered as a bolus, to assess blood volume, and to depict the architecture of tumour vasculature with improved spatial resolution. They can be used to more accurately measure tumour permeability, blood flow and extracellular volume with higher spatial resolution and without a requirement for very fast sequences. These applications are predominantly limited to pre-clinical studies, as most high molecular weight agents are not licensed for clinical applications as yet.

4. Imaging methods to assess signal change due to contrast agent delivery.

T1 weighted measurement methods are used to assess contrast uptake in tissues. Quantitative techniques are generally recommended(6;7), to aid intercomparison and transportability between centres. This should include an assessment of native tissue T1 relaxation time, so that measurement of signal changes is not biased by native T1. By measuring T1 relaxation times, contrast agent concentration can be derived, with a known relaxivity. Measurement methods include multi-point T1 weighted measurements, proton density and T1 weighted measurements(8-13). While these approaches generally correct for receive coil sensitivity, they can be affected by transmit coil response affecting flip angle, and methods that minimise for such sensitivity are advisable. 2D acquisitions allow more rapid measurements, but are generally limited to a few slices, and are affected by slice profile effects. Cross talk between slices can reduce sensitivity if line interleaved acquisitions are used(14). Calculation of contrast agent concentration and the accuracy of compartmental models can also be affected by water exchange(15). Measurement of arterial input function in a major vessel is difficult due to inflow and flow sensitivity effects. 3D acquisitions have limited temporal resolution, but are more robust with respect to slice profile and arterial input measurements. In all cases it is important to ensure that the sequence flip angle and repetition time are appropriate to the dynamic range of contrast agent concentration to be assessed. Care should be taken to minimise sensitivity to T2* effects. Measurements of larger molecular weight compounds may need to be tuned to the higher relaxivity of these agents, but the reduced requirements for time resolution may aid spatial resolution and volume coverage. Techniques developed for contrast-enhanced angiography may aid depiction of tumour vasculature.

Blood volume and perfusion measurements usually exploit T2* contrast mechanisms, relying on the loss of signal resulting from a high concentration of contrast. This usually requires high time resolution to capture the first pass(16). With blood pool agents, the effect will be retained in the longer term, allowing higher spatial resolution approaches, provided there is no local leakage of the agent, which would destroy the local susceptibility gradient. Dual echo techniques can allow both T1 weighted and T2* weighted contrast changes to be assessed simultaneously(11).

5. The trade-offs inherent in measuring contrast agent uptake by MRI.

Determining the optimum approach for a contrast enhanced study depends on many interdependent parameters concerned with equipment, volume coverage, information required, practicality in a clinical or experimental context and technology available. The balance between these parameters can depend on the anatomical location of

interest, and on the technology available. The major aspects governing the quality of the information obtained are the contrast to noise of the measurement (dependent on relaxivity, spatial and temporal resolution, contrast sensitivity and dynamic range, coil configuration), temporal resolution (flip angle, TR, TE, defines ability to assess initial uptake or first pass, volume coverage, spatial resolution, 2D/3D), spatial resolution (temporal resolution, volume coverage, slice thickness, contrast to noise), accuracy of quantification, flow sensitivity, motion sensitivity. Given that changes over time are being assessed, motion is a particular problem in the thorax and abdomen. Motion can often be reduced by using breath-hold acquisition, gating, triggering or navigator motion. However other involuntary motion such as GI tract motion, can present a more difficult problem.

6. What properties of tumours are measured.

MRI is becoming increasingly capable of depicting tumour vasculature, based on angiographic techniques. Resolution is limited by the spatial resolution of the imaging sequence (taking account also of slice thickness). Often this places a limit of 0.5-1mm, unless small field of view imaging is performed. In principle, if sufficient contrast in the vascular signal is available, the presence of structures below this resolution may be apparent, as is also the case for structures below the slice thickness. However these structures cannot be accurately spatially defined. Sensitivity is also limited in highly permeable tumours, as with small molecular weight contrast agents the enhancement of surrounding tumour will reduce the contrast with vessels. Blood pool agents, with limited leakage from tumour vasculature, can aid discrimination of vessels within tumours. These approaches with blood pool agents would allow assessment of blood volume(17). Those agents with detectable leakage can be used to assess tumour vascular permeability(18). T2* first pass techniques can allow estimation of relative blood volume, relative blood flow and mean transit time. In principle, quantitative measurements can be made, with knowledge of the arterial input function and normalisation factors that take account of factors such as relaxivity and local tissue haematocrit(19). T1 weighted measurements allow assessment of contrast agent delivery and leakage into the extra-cellular space. This can be used to identify areas of contrast extravasation, a common approach in tumour detection and diagnosis. Increasingly the signal enhancement characteristics are assessed, providing some information on the lesion characteristics. This information may be obtained in terms of the shape of the contrast curve, or metrics describing this such as rate of enhancement, time to maximum, amplitude of maximum. These measures are often sequence and equipment dependent, and can be difficult to translate between machines, but have been used for characterising abnormal tissues, and for assessing grade and response. Quantitative assessments of contrast uptake and washout behaviour calculate contrast agent concentration, based either on assumptions of linearity of signal change with contrast concentration, or on the use of calibrated measurement methods and a value for the relaxivity of the agent. These calculated values can be used directly (eg maximum value), integrated over a period (initial area under the gadolinium contrast curve - IAUGC) which is a robust non-model dependent descriptor, or fitted to a pharmacological model to derive physiological parameters. These approaches are also used for diagnosis, grading and assessment of response. They provide parameters such as K^{trans} – rate of transfer out of the vasculature, v_e – extra-cellular voulume, k_{ep} – transfer back to the vasculature (6;7;20). These are described in detail in a following lecture.

7. Examples of applications in cancer.

There are a very wide range of applications of these methods in cancer, both for experimental and for clinical studies. Detection of cancer, either in screening, targeted screening, or in identification of source of symptoms, increasingly is using contrast enhanced MR imaging. A particular example is the detection of early stage breast cancer, as a targeted screening application in high-risk women. Recent reports have shown MR to have a high sensitivity compared with conventional X-ray mammography in women at high risk of breast cancer (21-23). MR can also help discriminate benign from malignant disease on the basis of morphology and of contrast agent dynamics. Contrast enhanced imaging is used to help define the characteristics of disease in a range of conditions. In brain tumours, contrast enhanced imaging helps discriminate tumour type, and in astrocytoma helps distinguish low-grade disease from high-grade disease. A number of studies have shown that contrast agent uptake characteristics can predict response to therapy, presumably in part due to drug access, or relative hypoxia(24). Dynamic behaviour of contrast agent has been evaluated in many studies to assess response of tumour to a range of treatments. In prostate cancer for example, vasculature is under androgen control, and androgen blockade leads to much reduced contrast enhancement(25). Conventional chemotherapy can affect tumour vascular support, for example in breast cancer, changing contrast uptake and providing a measure of drug action. Changes in contrast observed with these treatments may reflect impact on vasculature, or on cell numbers due to the cytotoxic action of the drugs, and thus on the metabolic demand of the tumour. These changes may also affect tumour interstitial pressure, which can also affect access of contrast agent. Tumour vasculature, neo-angiogenesis and the processes supporting these structures and properties of tumours are major targets for novel cancer therapeutics. Dynamic contrast enhanced MR is now being used both in experimental research into these agents, the processes that control tumour vascularity, and in early clinical trials of new agents(26-34). Often quantitative measurement techniques are used, with contrast uptake parameters calculated for single volumes of interest, or on a pixel by pixel basis.

Reference List

(1) Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol 2002; 29(6 Suppl 16):15-18.

(2) Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer 2003; 3(6):401-410.

(3) McColl BK, Stacker SA, Achen MG. Molecular regulation of the VEGF family - inducers of angiogenesis and lymphangiogenesis. APMIS 2004; 112(7-8):463-480.

(4) Roberts TPL, Noseworthy MD. Contrast agents for magnetic resonance imaging. In: Jackson A, Buckley DL, Parker GJM, editors. Dynamic contrast enhanced magnetic resonance imaging in oncology. Berlin: Springer-Verlag, 2005: 23-37.

(5) Turetschek K, Preda A, Novikov V, Brasch RC, Weinmann HJ, Wunderbaldinger P et al. Tumor microvascular changes in antiangiogenic treatment: assessment by magnetic resonance contrast media of different molecular weights. J Magn Reson Imaging 2004; 20(1):138-144.

(6) Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A et al. Assessment of antiangiogenic and antivascular therapeutics using MRI: recommendations for appropriate methodology for clinical trials. Br J Radiol 2003; 76 Suppl 1:S87-91.:S87-S91.

(7) Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A et al. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: issues and recommendations. Br J Cancer 2005; 92(9):1599-1610.

(8) Brookes JA, Redpath TW, Gilbert FJ, Needham G, Murray AD. Measurement of spin-lattice relaxation times with FLASH for dynamic MRI of the breast. Br J Radiol 1996; 69(819):206-214.

(9) Parker GJ, Suckling J, Tanner SF, Padhani AR, Revell PB, Husband JE et al. Probing tumor microvascularity by measurement, analysis and display of contrast agent uptake kinetics. J Magn Reson Imaging 1997; 7(3):564-574.

(10) Parker GJ, Baustert I, Tanner SF, Leach MO. Improving image quality and T(1) measurements using saturation recovery turboFLASH with an approximate K-space normalisation filter. Magn Reson Imaging 2000; 18(2):157-167.

(11) d'Arcy JA, Collins DJ, Rowland IJ, Padhani AR, Leach MO. Applications of sliding window reconstruction with cartesian sampling for dynamic contrast enhanced MRI. NMR Biomed 2002; 15(2):174-183.

(12) Buckley DL, Parker GJM. Measuring contrast agent concentration in T1-weighted dynamic contrast enhanced MRI. In: Jackson A, Buckley DL, Parker GJM, editors. Dynamic contrast enhanced magnetic resonance imaging in oncology. Berlin: Springer-Verlag, 2005: 69-79.

(13) Gowland PA, Stevenson PL. T1: the Longitudinal Relaxation Time. In: Tofts PS, editor. Quantitative MRI of the brain: measuring change caused by disease. Chichester: John Wiley, 2003: 111-141.

(14) Brown J, Buckley D, Coulthard A, Dixon AK, Dixon JM, Easton DF et al. Magnetic resonance imaging screening in women at genetic risk of breast cancer: imaging and analysis protocol for the UK multicentre study. UK MRI Breast Screening Study Advisory Group. Magn Reson Imaging 2000; 18(7):765-776.

(15) Zhou R, Pickup S, Yankeelov TE, Springer CS, Jr., Glickson JD. Simultaneous measurement of arterial input function and tumor pharmacokinetics in mice by dynamic contrast enhanced imaging: effects of transcytolemmal water exchange. Magn Reson Med 2004; 52(2):248-257.

(16) Kennan RP, Jager HR. T2 and T 2* w DCEMRI: Blood Perfusion and Volume Estimation using Bolus
Tracking. In: Tofts PS, editor. Quantitative MRI of the brain: measuring change caused by disease. Chichester: John Wiley, 2003: 365-412.

(17) Jackson A. Imaging microvascular structure with contrast enhanced MRI. Br J Radiol 2003; 76 Spec No 2:S159-S173.

(18) Fournier LS, Brasch RC. The role of blood pool contrast media in the the study of tumour pathophysiology. In: Jackson A, Buckley DL, Parker GJM, editors. Dynamic contrast enhanced magnetic resonance imaging in oncology. Berlin: Springer-Verlag, 2005: 39-52.

(19) Calamante F. Quantification of dynamic susceptibility contrast T2* MRI in oncology. In: Jackson A, Buckley DL, Parker GJM, editors. Dynamic contrast enhanced magnetic resonance imaging in oncology. Berlin: Springer-Verlag, 2005: 53-67.

(20) Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV et al. Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols. J Magn Reson Imaging 1999; 10(3):223-232.

(21) Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004; 292(11):1317-1325.

(22) Kriege M, Brekelmans CT, Boetes C, Besnard PE, Zonderland HM, Obdeijn IM et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004; 351(5):427-437.

(23) Leach MO, Boggis CR, Dixon AK, Easton DF, Eeles RA, Evans DG et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005; 365(9473):1769-1778.

(24) George ML, Dzik-Jurasz AS, Padhani AR, Brown G, Tait DM, Eccles SA et al. Non-invasive methods of assessing angiogenesis and their value in predicting response to treatment in colorectal cancer. Br J Surg 2001; 88(12):1628-1636.

(25) Padhani AR, MacVicar AD, Gapinski CJ, Dearnaley DP, Parker GJ, Suckling J et al. Effects of androgen deprivation on prostatic morphology and vascular permeability evaluated with mr imaging. Radiology 2001; 218(2):365-374.

(26) Galbraith SM, Maxwell RJ, Lodge MA, Tozer GM, Wilson J, Taylor NJ et al. Combretastatin A4 phosphate has tumor antivascular activity in rat and man as demonstrated by dynamic magnetic resonance imaging. J Clin Oncol 2003; 21(15):2831-2842.

(27) Morgan B, Thomas AL, Drevs J, Hennig J, Buchert M, Jivan A et al. Dynamic contrast-enhanced magnetic resonance imaging as a biomarker for the pharmacological response of PTK787/ZK 222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases, in patients with advanced colorectal cancer and liver metastases: results from two phase I studies. J Clin Oncol 2003; 21(21):3955-3964.

(28) Jayson GC, Zweit J, Jackson A, Mulatero C, Julyan P, Ranson M et al. Molecular imaging and biological evaluation of HuMV833 anti-VEGF antibody: implications for trial design of antiangiogenic antibodies. J Natl Cancer Inst 2002; 94(19):1484-1493.

(29) Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003; 349(5):427-434.

(30) Padhani AR. MRI for assessing antivascular cancer treatments. Br J Radiol 2003; 76 Spec No 1:S60-S80.

(31) Mross K, Drevs J, Muller M, Medinger M, Marme D, Hennig J et al. Phase I clinical and pharmacokinetic study of PTK/ZK, a multiple VEGF receptor inhibitor, in patients with liver metastases from solid tumours. Eur J Cancer 2005; 41(9):1291-1299.

(32) Dowlati A, Robertson K, Radivoyevitch T, Waas J, Ziats NP, Hartman P et al. Novel Phase I Dose De-escalation Design Trial to Determine the Biological Modulatory Dose of the Antiangiogenic Agent SU5416. Clin Cancer Res 2005; 11(21):7938-7944.

(33) Thomas AL, Morgan B, Horsfield MA, Higginson A, Kay A, Lee L et al. Phase I study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of PTK787/ZK 222584 administered twice daily in patients with advanced cancer. J Clin Oncol 2005; 23(18):4162-4171.

(34) Liu G, Rugo HS, Wilding G, McShane TM, Evelhoch JL, Ng C et al. Dynamic contrast-enhanced magnetic resonance imaging as a pharmacodynamic measure of response after acute dosing of AG-013736, an oral angiogenesis inhibitor, in patients with advanced solid tumors: results from a phase I study. J Clin Oncol 2005; 23(24):5464-5473.